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Vaccination in patients with immunosuppression

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Abstract

In congenital or aqcuired immune deficiencies, infectious diseases which can be prevented by vaccination have a severe course because of supression of the immune system by the disease itself or the treatment methods used. Therefore, vaccination is important in immune deficiency. Although the protective antibody levels achieved in healthy individuals can not be provided in patients with immune deficiency, there is no drawback in administering inactive vaccines in accordance with the vaccination program. On the other hand, live viral and bacterial vaccines should not be administered during periods of immunosupression in conditions where the immune system is strongly supressed by diseases or drugs, since they would cause to systemic infection. Physicians should have sufficient knowledge about contraindications of vaccination in individuals with immune deficiency and in people who live in the same house with these individuals. (Türk Ped Arş 2014; 49: 181-5)

Key words: Live vaccines, immune deficiency, inactive vaccines, contraindication

The possibility of having diseases which can be prevented with vaccines and having a severe disease is high in patients with primary (deficiency of cellular immunity, humoral immunity or both) or secondary (acquired, suppression of the cellular/humaral immunity following morbidity or treatment) immunosupression. In patients with immune deficiency, the safety and efficiency of vaccines vary with the type and severity of immunosupression. Since studies related with efficiency and safety of vaccines in patients with immunosupression are limited and the guidelines related with administration of vaccines in these individuals are usually based on hypothetical information, "surveillance" studies should be pursued after vaccination. On the other hand, vaccination rates in individuals with immunosupression are not high because of insufficent knowledge of physicians about efficiency, safety and contraindications of vaccines (1).

Degree of immunosupression

Individuals with severe immunosupression: patients with combined primary immune deficiency (including severe combined immune deficiency), patients who receive cancer chemotherapy and/or radiotherapy, the first two months following solid organ transplantation, children with Human Immunodeficiency Virus (HIV) with CD4-T lymphocyte count below 15%, patients who have received high dose corticosteroids for a long term, individuals who receive biological immunomodulator agents. The degree of immunosupression in patients in whom hematopoetic stem cell transplantation has been performed varies according to the type of the donor, the type of transplantation (autologous, allogenic), problems which develop after transplantation and the treatment administered.

Individuals with mild immunosupression: individuals who have received steroids for a period shorter than 14 days and at a low dose (<20 mg), asymptomatic patients with HIV with a CD4-T lynphocyte count of 15-24%, patients who receive low dose methotrexate (MTX: ≤0.4 mg/kg/week), azathioprine ≤3 mg/kg/day, 6-mercaptopurine ≤1.5 mg/kg/day for maintenance chemotherapy for cancer (2).

Live vaccines

As a rule, severe systemic reactions may develop against vaccine strains in individuals with severe immunosupression and in individuals with unknown functions related with the immune system. Therefore, live viral vaccines (polio, MMR (measles,

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mumps, rubella), varicella) and live bacterial vaccines (BCG) should not be administered unless the individual is in the remission stage. However, some live vaccines can be administered safely in some immune system disorders or when the benefit of the vaccine outweighs the side effects.

Inactive vaccines

In primary and secondary immune deficiencies, all inactive vaccines (recombinant, subunit, toxoid, polysaccharride, conjugated polysaccharide vaccines), conjugated pneumococcal (CPV), tetanus-diphteria-acellular pertussis- hemophilus influenza type B (Hib) -inactive polio (DTaB-Hib-IPV), inactive influenza, tetanus-diphteria-acellular pertussis-inactive polio (DTaB-IPV), Hepatitis B, Hepatitis A)] can be administered in accordance with the child's vaccination schedule (1-4).

Diseases which cause to primary immune deficiency

Congenital immune deficiencies including complement deficiencies, phagocyte dysfunctions, cell receptor and signal transmission disorders, X-linked agammaglobulinemia which leads to antibody production failure, variable immune deficiencies, severe combined immune deficiency syndrome, complete Di George syndrome, Wiskott-Aldrich syndrome, adaptive immune deficiencies including ataxia-telangiectasia are very important causes of infections, morbidities and mortality. Inactive vaccines can be administered safely in these patients. Live vaccines should not be administered, since they may cause to severe systemic disease by way of viremia/bacteriemia. For example, oral polio vaccine (OPV) may lead to paralytic polio in humoral (B-lymphocyte) and combined immune deficiencies. Rotavirus vaccine is not recommended in primary and secondary immune deficiencies, since it is not safe. However, some authors recommend administration of OPV in individuals with HIV infection or who have had contact with HIV considering the benefits and risks. OPA should not be administered to the family members of these individuals. Inactive and live vaccines have been mostly administered to children with primary immune deficiency during infancy, since they are diagnosed lately because of the rarity of the disease. Immune deficiency should be considered, when systemic BCGitis occurs following administration of BCG. Live vaccines can be administered, if there is only IgA deficiency (4, 5).

There is no contraindication for inactive and live vaccines administered in accordance with the vaccination schedule in congenital complement deficiency including classical and alternative complement pathways including deficiency of C5-C9 complement component and factor H and D deficiency. These individuals should be vaccinated with conjugated Hib and conjugated meningococcal vaccine, since the risk of morbidity due to hemophilus influenza type B and meningocuccus will increase. Similarly, children with congenital immune deficiency should receive complete doses of Hib and conjugated pneumococcus, 4-component and 5-component combined vaccines (1, 2).

Varicella and MMR vaccines can be administered to children with chronic granulomatous disease, congenital and cyclic neutropenia and complement deficiency. However, live bacterial vaccines (BCG, thypoid fever) should not be administered in phagocyte dysfunction. Live vaccines preferably should not be administered in phagocyte dysfunctions including leukocyte adhesion defect and Chediak-Higashi and cytokine signal disorders (2, 4).

In asplenic patients and in patients in whom the spleen is dysfunctional, especially bacteriae with polysaccharide capsule cause to severe infections with a high mortality rate. Therefore, administration of vaccines for Hib, pneomococcus and meningococcus is important in these individuals. PCV-13 vaccine, Hib vaccine (included in the 5-component vaccine) and conjugated meningogoccus vaccine which are included in the vaccination program should be administered. These vaccines should be administered two weeks before operation in case of scheduled surgical splenectomy because of the disease (2).

All inactive vaccines including conjugated polysaccharide vaccines (penumococcus, Hib) and 4 and 5-component combined vaccines can be administered in conditions where B cell (antibody deficiency) and combined immune deficiency are present. However, vaccine protection is not good after vaccination in patients who receive immunoglobulin and in severe deficicency states. Live vaccines including varicella, OPV and MMR are not recommended in moderate-severe B cell immune deficiency, because response to vaccine is insufficient and severe side effects may be observed (2-4).

Vaccination of patients with immune deficiency is summarized in Table 1.

Patients with cancer

Cancer may decrease the protectivity of vaccines or inactivate vaccines directly with damage to the organ involved or indirectly with chemotherapeuticals, radiotherapy, blood products and monoclonal antibodies used. Generally, hematological cancers including leukemia and lymphoma affect the immune system of children with a higher rate compared to solid cancers. All available inactive vaccines provide the desired protective effect in children with cancer, though with a lower degree compared to individuals with healthy antibody levels. Polysaccharide or conjugated pneumococcal vaccine should not be administered to patients who receive blood products and monoclonal antibody (including rituximab) for at least 6 months. The number of doses of 4 and 5-component combined vaccines and hepatitis vaccines should be appropriate for the age. Since infections due to bacteriae with polysaccharide capsule have a severe course in patients who have undergone splenectomy because of morbidity, vaccines for pneumococcus and meningococcus should be repeated with certain intervals (five years) and Hib vaccines should be repeated until the age of 6 years in these children.

Table 1. Vaccine contraindications, efficiency and risks in immune deficiencies

Immune deficiency	Diseases	Vaccine contraindication	Efficiency, risks, interpretation[a]
Primary immune deficiencies			
B lymphocyte (humoral)	Severe antibody deficiencies (X-linked agammaglobulinemia, variable immune deficiency)	OPV, live influenza (LAIV), live bacteria (BCG, typhoid fever), MMR, varicella and rotavirus	The efficiency of vaccine is unclear, if dependent on only humoral response. Intravenous immunoglobulin affects the response to MMR and varicella vaccines negatively
	Mild antibody deficiency (selective IgA deficiency, Ig subgroup deficiency)	OPV, BCG. All other live vaccines can be administered	All vaccines are efficient, but the immune response may be weak
T lymphocyte (cellular)	Complete deficiency (severe combined immune deficiency, complete DiGeaorge syndrome)	All live vaccines	Inactive vaccines can be administered; all vaccines are probably inefficient/low efficiency
	Partial deficiencies (partial Di George syndrome, ataxia-telengiectasia, Wiskott-Aldrich syndrome)	All live vaccines	The efficiency of vaccine depends on the degree of immunosupression
Complement deficiency	Persistent complement deficiency, C5-C9, C3, properdin, factor B deficiency	None	All vaccines are efficient, pneumococcal and meningococcal vaccines should be absolutely administered
Fagocyte dysfunction	Chronic granulomatous disease, leukocyte adhesion defect, myeloperoxidase deficiency	Live bacterial vaccines (BCG, typhoid fever)	All inactive vaccines and other live vaccines (though less efficient) are efficient
Secondary immune deficiencies	Asplenia/functional asplenia	None	All vaccines are efficient, capsulated polysaccharide vaccines (pneumococcal, meningococcal, Hib) should be administered
	Chronic renal diseases	LAIV	Pneumococcal and Hepatitis B vaccines should be completed
	Cancer, organ transplantation, autoimmune disease, immunosupressive treatment, radiotherapy	Depending on the individual's immune status all live viral/bacterial vaccines	Vaccine efficiency depends on the immune status
	HIV/AIDS	OPV, BCG, MMRV, LAIV, if severe immunosupression is present MMR and varicella vaccines are not administered	MMR, varicella, rotavirus and all inactive vaccines are efficient Pneumococcal, meningococcal and Hib vaccines are beneficial

OPV: oral polio vaccine; LAIV: live attenuated influenza vaccine; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; BCG: live bacterial vaccines; Hib: hemophlus influenza type B; MMR: measles-mumps-rubella; [a]: all other vaccines in the Schedule can be administered

Diseases including measles and varicella have a severe course in patients with cancer. Since live viral vaccines will lead to viremia in the active period of the disease in cancer patients who receive chemotherapy or radiotherapy, these vaccines are not recommended in these patients and family members during this period. Varicella and MMR vaccines should be administered when the disease is in remission (three months after the drugs are discontinued at the earliest) or before chemotherapy. The same is also true for BCG vaccine (1-4).

Hematopoetic stem cell transplant recipients

The immunity against diseases in hematopoetic stem cell transplant recipients is affected by the transplantation type (autologous or allogenic stem cell transplantation), the immunosupressive drugs used, the time passed after transplantation and organ rejection. The vaccines administered previously in accordance with the vaccination schedule should be repeated, since the immune system is supressed to a great extent after stem cell transplantation and the immune memory is lost. If it is time to administer a live vaccine according to the vaccination schedule before transplantation, it should be administered 4 weeks before transplantation at the earliest. All inactive vaccines which have not been administered before can be administered after transplantation. 4 and 5-component combined vaccines, dT can be administered 6 months after transplantation and CPV, meningococcal vaccive and seasonal influenza vaccine can be administered 3-6 months after transplantation. Hepatitis B vaccines can be administered without waiting after transplantation. Hepatitis A vaccine can be administered 12 months after transplanta-

tion. Varicella and MMR vaccines should be administered 24 months after transplantation. These live vaccines should not be administered, if the transplanted organ is rejected. BCG vaccine should not be administered in these patients, since T cell functions are very insufficient. Although the risk of cytomegalovirus infection is high in transplant patients, there is no licensed vaccine against cytomegalovirus yet (1, 6).

Solid organ transplant recipients

Vaccination is necessary in organ transplant recipients, since catching infection will be easy because of immunosupression due to present organ failure, rejection of the transplanted organ and immunosupressive drugs used after transplantation. In these patients, inactive vaccines appropriate for the age should be administered 2 weeks before transplantation and varicella, OPV and MMR vaccines should be adminsitered 1 month before transplantation. There is no clear data about when to vaccinate unvaccinated individuals or individuals with incomplete vaccination after transplantation. However, as mentioned above, all inactive vaccines included in the vaccination schedule can be administered. These vaccines are reccomended to be administered 6 months after transplantation when the immune system is supressed relatively less. Primary doses can be administered before transplantation and rapel doses can be administered after transplantation. Since hepatitis A and hepatitis B have a severe course in organ transplant recipients, it should be ensured that hepatitis A and hepatitis B vaccinations are completed. Conjugated pneumococcal vaccine (CPV-13) can be administered both as the primary dose and rapel dose. Polysaccharide vaccine (PPS 23) can be used as a repeated dose after two years of age and after conjugated vaccine. Live vaccines should not be administered, since immunosupressive drugs are given after transplantation (1, 2, 7).

Individuals with chronic inflammatory disease

In rheumatic, neurological, hematological and gastrointestinal chronic inflammatory diseases, the immune response against vaccines and side effects of vaccines may show difference compared to healthy individuals because of the properties of the disease (exacerbation-remission) and various immunosupressive drugs, monoclonal antibodies and biological agents used. Although the protective antibody level is lower compared to healthy individuals, inactive vaccines are not contraindicated in patients with chronic inflammatory disease. Conjugated vaccines including pneumococcal, Hib and meningococcal vaccines can be administered. Other inactive vaccines should be administered in accordance with the vaccination schedule as in healthy children. Live vaccines (varicella, MMR, oral polio) should not be administered under intensive immunosupressive treatment and if severe immunosupression due to the disease is present. These vaccines are administered in the remission phase of the disease. Low dose corticosteroid treatment (up to 20 mg/day)is not an obstacle for administration of live vaccine. Live vaccines can be administered in individuals with HIV infection without severe immunosupression. Hepatitis A and B vaccines should be completed in patients with chronic liver disease (1-3, 8, 9).

Individuals who receive biological agents to decrease inflammation

These new drugs which are usually known as cytokine inhibitors are used as immunomodulators in combination with other immunosupressive drugs in various chronic inflammatory diseases including mainly juvenile idiopathic arthritis and inflammatory bowel disease with a gradually increasing frequency in recent years. These drugs which act as antibodies against proinflammatory cytokines decrease inflammation by affecting cytokine receptors. Their action of immunomodulation continues weeks after continuation of treatment. These drugs facilitate pathogenity and/or reactivation of microorganism for which the cellular immunity should be effective including mainly intracellular bacteriae and weaken the individual's cellular immunity. Inactive and live vaccines should have been completed in these individuals. MMR and varicella vaccines should not be administered in the patients who receive these agents at least for 6 months (1, 2, 10, 11).

Individuals who use corticosteroids

The degree of immunosupression due to the disease, other immunosupressive drugs used simultaneoulsy and the amount and usage period of corticosteroids affect the predisposition to infections and response to vaccines. A steroid (prednisolone or equivalent) dose higher than 2 mg/day or steroid treatment at a dose of more than 20 mg and with a period longer than 14 days in children weighing more than 10 kg cause to immunosupression. Live vaccines should not be administered in these individuals until at least one month after steroid discontinuation. Lower doses with shorter periods than mentioned above, topical, local or aerosol steroid usage are not contraindications for live vaccines during the period of treatment. In cases where other immunosupresive drugs are used simultaneously, live vaccines should be administered after discontinuation of these therapies (3 months at the earliest) (2).

Indiviuals who receive intravenous immunoglobulin (IVIG) and other blood products

The efficiency of live virus vaccines may decrease, if administered before two weeks of administration of IVIG (standard or hyperimmunglobulin) or in 1-2 months after administration of IVIG. Since IVIG supresses especially the response to measles vaccine for a very long time depending on the dose, MMR vaccine should be administered 8 months after administration of IVIG. Although the effect of IVIG treatment on varicella vaccine is not known fully, it should be postponed 8 months as with MMR vaccine. If MMR and varicella vaccines have been administered within 14 days before IVIG, they should be repeated after IVIG (8 months). Transfusion of washed erithyrocyte suspension does not postpone ad-

ministration of live vaccine. However, MMR and varicella vaccines should be administered three months after (other) erithyrocyte suspension transfusion, 6 months after whole blood transfusion and 7 months after plasma and platelet transfusion. Since oral polio vaccine, rotavirus, live influenza virus, all inactive vaccines are not affected by blood and blood product transfusions, they can be administered in accordance with the vaccination schedule (1, 4).

Family members of individuals with immune deficiency

There is no drawback to administer all vaccines (including rotavirus) except for OPV to family members of children with primary or secondary immune deficiency. Care should be taken to complete vaccination in family members including mainly the siblings (1-5).

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